PEDIATRIC PHARMACOTHERAPY

A Monthly Newsletter for Health Care Professionals from the Children's Medical Center at the University of Virginia

Volume 9 Number 11 November 2003

The Use of Melatonin in Children with Sleep Disturbances

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The administration of exogenous melatonin has been used in a variety of clinical settings, most frequently in the management of sleep disturbances, including insomnia and jet lag. Although considered a dietary supplement and not regulated by the Food and Drug Administration (FDA), melatonin was classified as an orphan drug by the FDA in November 1993 for the entrainment of circadian rhythm in blind people. In children, melatonin has been used for chronic insomnia, as well as in the management of sleep disturbances associated with vision disturbances, attention deficit/hyperactivity disorder (ADHD), and neurologic injury.[1-3]

Pharmacology

Melatonin (N-acetyl-5-methoxytryptamine) is a chronobiotic, a neurohormone involved in the regulation of the sleep-wake cycle. It is produced in the pineal gland through the conversion of tryptophan, first to serotonin, then N-acetylserotonin, and finally to melatonin. Melatonin is normally secreted during darkness, in response to the release of norepinephrine from retinal photoreceptors and the resulting activation of the retino-hypothalamic-pineal system. Levels begin to rise at nightfall, with peak serum concentrations typically occurring between 2 and 4 AM in adults. Secretion during daylight is minimal.[3]

Melatonin promotes sleep through regulation of the activity of the suprachiasmatic nucleus (SCN), located within the anterior hypothalamus above the optic chiasm. Impairment of melatonin production, secretion, or binding within the SCN may lead to chronic disturbances in both sleep onset and duration. In these patients, exogenous melatonin may be beneficial to regulate the sleep-wake cycle. Exogenous melatonin was first synthesized over two decades ago. It produces the same effects and is metabolized in the same manner as the endogenous neurohormone.[1-3]

Pharmacokinetics

After oral administration of exogenous melatonin, peak concentrations are achieved within 60 minutes. Melatonin is hepatically metabolized, with 80 to 90% converted to sulphatoxymelatonin (aMT6), an inactive compound which is excreted in the urine. The average elimination half-life of melatonin in adults is 20 to 50 minutes. The administration of exogenous melatonin does not appear to affect endogenous production or secretion.[2]

Use in Children

Since the first case report by Palm and colleagues in 1991,[4] there have been over two dozen papers describing the use of melatonin in children with sleep disturbances. Several studies have been published by Jan and colleagues of the Children's Hospital Visually Impaired Program at British Columbia's Children's Hospital. In 1994, they published a study of 15 children (ages 6 months to 14 years) given melatonin for sleep disturbances.[5] All of the subjects had failed to respond to traditional therapy, including nonpharmacologic measures to improve sleep hygiene. Nine of the patients had mental retardation, and two had ADHD. Nine children had either ocular or cortical vision impairment. The study was a double-blind crossover randomized design, with each child receiving melatonin at a dose of 2.5 to 5 mg or placebo at bedtime for a period of 7 to 10 days, then switching to the alternative arm after a 4 to 5 day wash-out period. Sleep diaries were maintained by the subjects' careproviders. Patients responding to therapy remained on melatonin after completion of the study and were followed at three and six months.

Thirteen of the 15 children had a favorable response to melatonin, with improvement in sleep duration. All of the subjects experienced clinical benefit, with improved daytime mood and behavior. Children with delayed sleep onset experienced the greatest response. The effective

dose ranged from 2.5 to 10 mg; higher doses or the administration of a second dose during the night produced no additional benefit. Ten of the patients continued on therapy after conclusion of the study, for periods up to a year. No adverse effects related to melatonin were reported.

Building on their initial case report, Palm and colleagues published the results of an open study of melatonin in eight blind children and young adults in 1997.[6] The patients ranged in age from 3 to 23 years of age, and all had significant sleep disturbances. Serum and urine concentrations of melatonin were evaluated in five patients prior to treatment, revealing delays in the time of peak concentrations (range 03:00 to 12:00). Administration of melatonin in doses of 0.5 to 4 mg produced improvement in all patients. Benefit was maintained long-term, up to six years in some patients. No adverse effects were reported.

Further support for the use of melatonin was added by Pillar and colleagues in their 1998 case report.[7] The patient was a 13 year old girl with psychomotor retardation and a one year history of an irregular sleep-wake cycle. Serial measurements of urine aMT6 were abnormally low, with no time-related differences indicating nocturnal release of melatonin. Actigraph recordings revealed no discernible night/day differentiation in sleep patterns. Administration of 3 mg melatonin nightly produced an immediate improvement in her sleep-wake cycle with an increase in total nocturnal sleep from an average of 5.5 to 7.7 hours and a reduction in daytime sleep from 4.4 to 2.8 hours. Urine nocturnal aMT6 levels measured one month after starting therapy showed a distinct increase at night, with a peak at 22:00.

During 2001, two studies of melatonin were published in the *Journal of Child Neurology*.[8,9] In February, Smits and coworkers reported their randomized, placebo-controlled trial of melatonin in 40 children (6 to 12 years of age) with chronic insomnia.[8] The children were randomized to receive either 5 mg melatonin or placebo, given nightly at 6 PM over a 4 week treatment period. At the conclusion of the study, patients could be continued on therapy if desired by the parents. Both sleep diaries and actigraph recordings were used to assess efficacy. Sleep onset and duration were significantly improved in the melatonin group, but showed no difference in the placebo group. Sleep latency, wake-up times, and sustained attention reaction times were not affected. Two children had headaches for the first two days of melatonin treatment. After 18 months, 13 of the 38 children evaluated had discontinued therapy without the return of insomnia. In one child, melatonin was stopped due to lack of effect. One child developed generalized epilepsy 4 months into the study, but causality with melatonin was not suggested.

Later that year, Dodge and Wilson published an additional randomized, double-blind, placebo-controlled, cross-over trial of melatonin in 20 children with developmental disabilities.[9] The melatonin dose was 5 mg in all children. In 18 of the subjects, time to sleep onset was significantly shorter with melatonin than placebo. The duration of sleep was greater than baseline values during melatonin treatment, but the difference between the melatonin treatment period and placebo was not statistically significant. The authors also failed to find a difference in the number of nighttime awakenings. They reported no adverse effects.

In 2002, Ross and colleagues published an observational study of melatonin administration in 49 children with neurodevelopmental disorders.[10] The patients ranged in age from 1 to 13 years, and the most frequent underlying illness was epilepsy. Patients less than 5 years of age were started on a dose of 2.5 mg nightly, while older children were started on 5 mg. Doses were increased by 2.5 mg increments at 3 day intervals until the desired effect on sleep patterns was achieved or the patients reached the maximum dose (7.5 mg in patients less than 2 years or 10 mg in older children). Of the 46 patients with evaluable sleep diaries or case notes, 34 (69%) showed improvement after receiving melatonin. In the 28 children with complete diaries, total sleep, nighttime sleep, duration and number of interruptions, and time of sleep onset improved with melatonin. The median sleep time increased from 54 to 65.5 hours/week after treatment. The median number of interruptions in sleep decreased from 7 to 3.5.

Melatonin appears to be beneficial in the management of the delayed sleep onset and frequent awakenings observed with other neurologic illnesses as well. Additional papers have noted the efficacy of melatonin in sleep disturbances associated with Rett syndrome and tuberous sclerosis, as well as in a child with a pineal tumor.[11-13] In a double-blind, placebo-controlled cross-over study of nine girls with Rett syndrome, melatonin in doses of 2.5 to 7.5 mg nightly produced significant benefits in sleep characteristics.[11] Sleep latency decreased from 42.1$\pm$12.0 (mean$\pm$SE) to 19.1$\pm$5.3 minutes during the first three weeks. Total sleep duration also improved, but the difference from baseline was not statistically significant.

In the January/February 2003 issue of *Clinical Pediatrics*, Ivanenko and colleagues from Kosair Children's Hospital Research Institute at the University of Louisville published a retrospective review of 32 children treated with melatonin in their program.[1] All had been referred to their sleep program after failure to benefit from conventional treatments. The children ranged in age from 2 to 18 years (mean 9.6±4.5 years). Several children had comorbidities, including ADHD (in 44% of subjects), anxiety (25%), affective disorders (9%), and mild developmental delay (9%).

Twenty-nine (90.6%) of the children experienced benefit from melatonin, with improvement in sleep onset and/or sleep maintenance. Average time to sleep onset, based on caregiver journals, declined from 90±52.5 to 25.4±11 minutes, and nocturnal awakenings declined from 18.7±15 to 1.2±2 times per week. The patients were treated with an average melatonin dose of 2.0±1.2 mg (range 0.3 to 6 mg), given one hour before bedtime. There was a positive relationship between patient age and dose, with the 2 to 6 year old group requiring an average dose of 1.4±0.6 mg and the 12 to 18 year olds requiring 2.8±1.4 mg. Although many caregivers reported clinical improvement within days of the initiation of therapy, normal sleep patterns were usually achieved within 1 to 2 weeks. The average duration of follow-up was 2 months, with the longest follow-up at 10 months. Melatonin was stopped in three patients due to lack of sustained response. No adverse effects were noted.

Earlier this month, Smits and colleagues published another study of melatonin for pediatric insomnia.[14] Building on the positive response in behavior reported by parents in their earlier study, the authors conducted a similar randomized, double-blind placebo-controlled trial in 62 children (6 to 12 years in age). Patients received either 5 mg melatonin or placebo at 7 PM for 4 weeks. In addition to standard measurements of sleep characteristics, health status was evaluated with the RAND General Health Rating Index (RAND-GHRI) and Functional Status II (FS-II) questionnaires. Total scores for both measures improved significantly more in the melatonin group than with placebo. The standardized response means for the RAND-GHRI were 0.69 in the melatonin group versus 0.07 in the controls, with FS-II scores of 1.61 versus 0.64. Melatonin advanced sleep onset by an average of 57 minutes, and salivary measurement of melatonin production showed an onset occurring an average of 82 minutes earlier during melatonin administration.

Drug Interactions

Melatonin has been reported to interfere with the antihypertensive effect of extended-release nifedipine.[2] The mechanism of this interaction has not been determined.

Adverse Effects

Exogenous melatonin appears to be well tolerated. In most clinical trials and case series, no adverse effects have been noted. Headache, excessive sedation, and transient depression have been reported, most often with doses greater than 8 mg/day. Isolated cases of rash, a psychotic episode, gynecomastia, and autoimmune hepatitis have also been reported after melatonin use, but in none of these cases has melatonin been identified as the cause.[1-3]

In a 1998 study published in *Lancet*, melatonin administration to six children with underlying seizure disorders produced a worsening of seizures in three.[15] Although this finding has not been reported in other papers, the benefit to risk ratio of melatonin in patients with seizures should be carefully weighed before initiation of therapy. Because melatonin may also play a role in immune function, it is not recommended for patients with autoimmune disorders.[2]

Dosing

Based on the case series and clinical trials published to date, melatonin should be initiated at a dose of 2.5 to 5 mg in children with sleep disturbances. The dose should be administered in the evening, approximately 30 to 60 minutes before bedtime. Dose titration should be based on response.[1-14] Some authors have noted that children with neurologic injury may require higher doses. In patients with nighttime awakenings, a controlled release dosage form may be more effective than standard immediate release products.[16]

Availability and Cost

Melatonin is available at most pharmacies and health food stores. It is manufactured as both immediate release and controlled release tablets and capsules. The most commonly available dosage strengths are 300 mcg, 1, 3, and 5 mg. In the Charlottesville area, the cost of a 60-tablet bottle (3 mg tablets) ranges from $3 to $8.

Melatonin is not considered a drug product, and is not regulated by the FDA. Patients and their families should be instructed to purchase only synthetic melatonin, rather than the bovine-derived product, in order to avoid potential exposure to infectious agents. In addition, careproviders should be aware of the potential for variation in content among brands, as well as

the presence of contaminants. A voluntary verification program has been developed by the United States Pharmacopeia (USP) to provide consumers with information on the quality of dietary supplements such as melatonin. The "USP verified" symbol on these products, while not a guarantee of efficacy or safety, indicates compliance with accepted manufacturing practices and standardization of contents.

Summary

Endogenous melatonin plays an important role in the regulation of the sleep-wake cycle. In children with sleep disturbances, the administration of exogenous melatonin appears to reduce the time to sleep onset and minimize nighttime awakenings. Melatonin is generally well tolerated, with few reports of adverse effects. In patients for whom traditional pharmacologic and nonpharmacologic therapies to improve sleep have failed, melatonin may be a useful adjunctive therapy.

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Pharmacology Literature Review

Cardiopulmonary Effects of Naloxone

Although frequently used to reverse opioid adverse effects in pediatric patients, little is known of the adverse effect profile of naloxone at standard doses. The authors of this study summarize their experience with naloxone in 195 children over a 3 year period. The average age of the patients was 9.7±6 years, and the total naloxone dose given ranged from 0.001 to 0.5 mg/kg, with a median dose of 0.1 mg. Compared to pretreatment values, respiratory rate, heart rate, and systolic and diastolic blood pressures were increased after naloxone administration. Transient systolic hypertension occurred in 33 of the patients (16.9%), while diastolic hypertension occurred in only 13 (6.6%) of the children. All cases of hypertension resolved without intervention. The only other adverse effect noted was a single case of pulmonary edema requiring positive pressure ventilation. Hasan RA, Benko AS, Nolan BM, et al. Cardiorespiratory effects of naloxone in children. **Ann Pharmacother 2003;37:1587-92.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee during their meeting on 10/24/03:

1. An inhaler containing the combination of fluticasone and salmeterol (Advair Diskus®) was added to both the Inpatient and Outpatient Formularies. It is indicated for the management of asthma in patients 12 years of age or older.
2. Influenza virus vaccine live, intranasal (FluMist®) and rosuvastatin (Crestor®), an HMG-CoA reductase inhibitor, were rejected.

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